

Tissue oxygen saturation during hyperthermic progressive central hypovolemia

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Schlader ZJ, Rivas E, Soller BR, Convertino VA, Crandall CG. Tissue oxygen saturation during hyperthermic progressive central hypovolemia. *Am J Physiol Regul Integr Comp Physiol* 307: R731–R736, 2014. First published July 16, 2014; doi:10.1152/ajpregu.00190.2014.—During normothermia, a reduction in near-infrared spectroscopy (NIRS)-derived tissue oxygen saturation (So₂) is an indicator of central hypovolemia. Hyperthermia increases skin blood flow and reduces tolerance to central hypovolemia, both of which may alter the interpretation of tissue So₂ during central hypovolemia. This study tested the hypothesis that maximal reductions in tissue So₂ would be similar throughout normothermic and hyperthermic central hypovolemia to presyncope. Ten healthy males (means ± SD; 32 ± 5 yr) underwent central hypovolemia via progressive lower-body negative pressure (LBNP) to presyncope during normothermia (skin temperature ≈34°C) and hyperthermia (+1.2 ± 0.1°C increase in internal temperature via a water-perfused suit, skin temperature ≈39°C). NIRS-derived forearm (flexor digitorum profundus) tissue So₂ was measured throughout and analyzed as the absolute change from pre-LBNP. Hyperthermia reduced ($P < 0.001$) LBNP tolerance by 49 ± 33% (from 16.7 ± 7.9 to 7.2 ± 3.9 min). Pre-LBNP, tissue So₂ was similar ($P = 0.654$) between normothermia (74 ± 5%) and hyperthermia (73 ± 7%). Tissue So₂ decreased ($P < 0.001$) throughout LBNP, but the reduction from pre-LBNP to presyncope was greater during normothermia (−10 ± 6%) than during hyperthermia (−6 ± 5%; $P = 0.041$). Contrary to our hypothesis, these findings indicate that hyperthermia is associated with a smaller maximal reduction in tissue So₂ during central hypovolemia to presyncope.

lower body negative pressure; heat stress; simulated hemorrhage; syncope

HEMORRHAGE, AND SUBSEQUENT cardiovascular decompensation, is a leading cause of death in both civilian and military settings (3, 14). That said, up to 25% of battlefield deaths are potentially survivable if adequate detection, intervention, and treatment is provided, with ~85% of those being hemorrhage-related (8, 16). Surviving a hemorrhagic injury is extremely time-sensitive (3). Thus, early recognition of the severity of the injury and rapid medical intervention is vital to patient survival (17). Unfortunately, changes in traditional hemodynamic markers (e.g., blood pressure and heart rate) during a hemorrhagic event are often late indicators of cardiovascular instability and are, therefore, poor survival prognosticators (5). Interestingly, Soller et al. (21, 22) identified that tissue oxygen

saturation (So₂), in the region of skeletal muscle, determined noninvasively via near-infrared spectroscopy (NIRS), is reduced during the initial stages of graded lower body negative pressure (LBNP), a hemorrhage model (11). In the absence of changes in metabolism, when blood flow under the measurement area is reduced, an increase in oxygen extraction ensues that is reflected in proportional reductions in tissue So₂ (2). Thus, reductions in tissue So₂ during LBNP reflect the magnitude of reductions in muscle blood flow in the measurement area (21, 22). Importantly, these LBNP-induced reductions in tissue So₂ occur prior to changes in blood pressure and heart rate and reflect the onset and the magnitude of reductions in stroke volume (21, 22). This is notable given that stroke volume is an index of the degree of central hypovolemia, but it is challenging to accurately measure in the field. Thus, noninvasive monitoring of tissue So₂ appears to be an early indicator of central hypovolemia in humans, suggesting it may be a valuable tool for monitoring the severity of blood loss during a hemorrhagic injury in prehospital and/or field settings.

Hyperthermia (i.e., increases in internal and skin temperatures) universally decreases tolerance to a simulated hemorrhagic insult (19), suggesting that the timeline to begin treatment is shortened during such conditions. Notably, early, noninvasive indicators of central hypovolemia during hyperthermia have not been determined. Therefore, the objective of this study was to test the hypothesis that, relative to that occurring during normothermia, hyperthermia will not affect the magnitude of maximal reductions in tissue So₂ occurring during LBNP to presyncope. The testing of this hypothesis will provide data regarding the utility of tissue So₂ as an early indicator of the severity of hemorrhage-induced central hypovolemia while hyperthermic. Such information could dictate medical treatment decisions made in prehospital and/or field settings. These findings have implications for conditions in which individuals are often hyperthermic and at an increased risk of a hemorrhagic injury (e.g., soldiers, miners, and firefighters).

METHODS

Subjects. Ten healthy, physically active, males participated in this study. The subject characteristics were (means ± SD) the following: age, 32 ± 5 yr; height, 183 ± 9 cm; and weight, 85.1 ± 12.5 kg. All subjects were nonsmokers, not taking medications, and were free of any known cardiovascular, metabolic, neurological, or psychological diseases. Each subject was fully informed of the experimental procedures and possible risks before giving informed, written consent. This protocol and informed consent were approved by the Institutional

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Review Boards at the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital of Dallas, and all procedures conformed to the standards set by the Declaration of Helsinki. Subjects arrived at the laboratory euhydrated (confirmed via a urine-specific gravity <1.025) and having refrained from strenuous exercise, alcohol, and caffeine for a period of 24 h. Testing was completed in the northern hemisphere (Dallas, Texas) during fall, winter, and spring months.

Instrumentation and measurements. Approximately 60 min prior to experimental testing, each subject swallowed a telemetry pill (HQ, Palmetto, FL) for the measurement of intestinal temperature. Mean skin temperature was measured as the weighted average of six thermocouples attached to the skin. Body temperature was controlled via a water-perfused tube-lined suit (Med-Eng, Ottawa, ON, Canada) that covered the entire body except the head, hands, one forearm, and the feet. Heart rate was continually recorded from an electrocardiogram (HP Patient Monitor, Agilent, Santa Clara, CA) interfaced with a cardiometer (CWE, Ardmore, PA). Beat-to-beat blood pressure was continuously measured via the Penaz method (Finometer Pro, FMS, Amsterdam, The Netherlands), which was confirmed intermittently via auscultation of the brachial artery by electrospigmomanometry (Tango+, SunTech, Raleigh, NC). Tissue SO_2 was measured noninvasively using NIRS (CareGuide 1100, Reflectance Medical, Westborough, MA). This NIRS device uses a novel sensor design and mathematical preprocessing techniques to correct spectra for variations in skin pigment and fat prior to the calculation of tissue SO_2 (9). The NIRS sensor was placed on the left forearm over the flexor digitorum profundus in the longitudinal axis with the head of the sensor nearest to the olecranon process and secured against the skin with custom adhesive pads.

Experimental protocol. Subjects visited the laboratory on two separate occasions, separated by at least 8 wk, but completed at the same time of day (within a subject). During both trials, following instrumentation, subjects rested quietly in the supine position for at least 45 min, while normothermic water (34°C) perfused the suit. After baseline data collection, subjects underwent either whole body passive heat stress or a normothermic time control period, the latter of which was 40–60 min in duration. Whole body passive heat stress was induced by perfusing 49°C water through the suit that was sufficient to increase internal temperature $\sim 1.2^\circ\text{C}$ above baseline, while 34°C water was perfused through the suit throughout the normothermic, time control trial. The subjects were not allowed to drink fluids at any time during either trial. Both trials were conducted in a randomized, counterbalanced manner. Immediately following the heating/time control period, the subjects underwent progressive LBNP to presyncope. LBNP commenced at 20 mmHg, with the level of LBNP increasing by 10 mmHg every 3 min until the onset of syncope signs and symptoms: continued self-reporting of feeling faint, sustained nausea, rapid and progressive decreases in blood pressure, resulting in sustained systolic blood pressure being <80 mmHg, and/or relative bradycardia accompanied with a narrowing of pulse pressure. Notably, every LBNP trial was terminated due to hemodynamically identified syncope signs.

Data and statistical analyses. Most data were collected at 50 Hz via a data acquisition system (Biopac System, Santa Barbara, CA), the exception being the NIRS tissue SO_2 data, which were sampled every 30 s. Steady-state data (3-min average) were analyzed at baseline (i.e., prethermal perturbation) and just prior to commencing LBNP (i.e., postthermal perturbation or time control period; Pre-LBNP). During LBNP, data (2-min average) were statistically compared between thermal conditions at 20 mmHg LBNP ($n = 10$), 30 mmHg LBNP ($n = 9$, due to poor NIRS signal in one subject), and 40 mmHg LBNP ($n = 5$, due to presyncope occurring at 30 mmHg during hyperthermia in an additional four subjects). Data were also analyzed at presyncope in both trials, regardless of the LBNP stage (1-min average; presyncope; $n = 9$) and at the same level of normothermia LBNP as that occurring at hyperthermia presyncope (mean LBNP level: 40 ± 10 mmHg; $n = 9$), i.e., the highest common LBNP stage between thermal conditions for each subject. Muscle metabolism changes minimally during hyperthermia under resting conditions (18), and therefore, changes in NIRS tissue SO_2 reflect the magnitude and direction of changes in tissue perfusion (2). Since perfusion through a vascular bed is governed, in part, by perfusion pressure, an index of tissue vascular conductance (tVC) was calculated as the quotient of tissue SO_2 and mean arterial pressure. To evaluate the isolated effect of LBNP, both with and without hyperthermia, data were also analyzed as the change from Pre-LBNP.

Baseline, Pre-LBNP, and during LBNP (20–40 mmHg LBNP) data were analyzed using two-way (main effects: trial \times time) repeated-measures ANOVA. Data at normothermia presyncope, hyperthermia presyncope, and normothermia 40 ± 10 mmHg LBNP (i.e., the same normothermia LBNP as that occurring at hyperthermia presyncope) were analyzed using one-way repeated-measures ANOVA. Where appropriate, post hoc Holm-Sidak pair-wise comparisons were made. Data were analyzed using SigmaPlot (v.12, Systat Software, Chicago, IL) with a priori statistical significance set at $P \leq 0.05$. All data are reported as means \pm SD.

RESULTS

Responses to hyperthermia alone. Baseline internal and mean skin temperatures were not different ($P \geq 0.498$) between trials (Table 1). Whole body passive heat stress increased ($P < 0.001$) both intestinal and mean skin temperatures by $1.2 \pm 0.1^\circ\text{C}$ and $5.1 \pm 0.1^\circ\text{C}$, respectively, whereas temperatures remained unchanged throughout the normothermia trial ($0.0 \pm 0.2^\circ\text{C}$ and $0.0 \pm 0.7^\circ\text{C}$, $P \geq 0.217$). Mean arterial pressure slightly increased ($P = 0.013$) from baseline to Pre-LBNP during the normothermia trial, but was unchanged ($P = 0.097$) during the hyperthermia trial (Table 1). Tissue SO_2 increased ($P = 0.009$) from baseline to Pre-LBNP in both trials (Table 1), while the magnitude of this increase was not different ($P = 0.593$) between trials. During normothermia, tVC did not change ($P = 0.994$) from baseline to

Table 1. Thermal and hemodynamic responses from baseline to Pre-LBNP during the normothermia and hyperthermia trials

	Normothermia		Hyperthermia	
	Baseline	Pre-LBNP	Baseline	Pre-LBNP
Intestinal temperature, $^\circ\text{C}$	37.0 ± 0.2	37.0 ± 0.3	36.9 ± 0.1	$38.1 \pm 0.1^{*}\dagger$
Mean skin temperature, $^\circ\text{C}$	34.1 ± 0.5	34.2 ± 0.7	34.0 ± 0.3	$39.1 \pm 0.7^{*}\dagger$
Heart rate, bpm	58 ± 8	62 ± 9	59 ± 8	$99 \pm 16^{*}\dagger$
Mean arterial pressure, mmHg	82 ± 6	$87 \pm 8^\dagger$	80 ± 7	77 ± 6
Tissue SO_2 , %	70 ± 4	$74 \pm 5^\dagger$	68 ± 4	$73 \pm 7^\dagger$
tVC (%/mmHg)	0.86 ± 0.07	0.86 ± 0.11	0.86 ± 0.10	$0.95 \pm 0.11^{*}\dagger\#$

Tissue SO_2 , near infrared spectroscopy-derived tissue oxygen saturation; tVC, tissue vascular conductance. * Significantly different from normothermia ($P < 0.001$). † Significantly different from baseline ($P \leq 0.047$). $\#$ Significantly different from normothermia ($P = 0.054$).

Pre-LBNP, but increased ($P = 0.047$) during this period during hyperthermia.

Responses to hyperthermic LBNP. LBNP time to tolerance (normothermia: 16.7 ± 7.9 min; hyperthermia: 7.2 ± 3.9 min) and the final LBNP stage reached (normothermia: 70 ± 20 mmHg; hyperthermia: 40 ± 10 mmHg) were higher ($P < 0.001$) during the normothermia trial. During hyperthermia, mean arterial pressure decreased ($P < 0.001$) during 20 through 40 mmHg LBNP, but not at these LBNP stages during normothermia (Fig. 1). Absolute mean arterial pressure and reductions (relative to Pre-LBNP) in mean arterial pressure at presyncope were not different ($P \geq 0.121$) between thermal conditions (Fig. 1). However, mean arterial pressure at normothermia 40 ± 10 mmHg LBNP was higher ($P \leq 0.007$) than this value when subjects were at presyncope during both normothermia and hyperthermia (Fig. 1). Heart rate was 30–40 bpm higher ($P < 0.001$) throughout hyperthermia prior to LBNP and increased ($P < 0.001$) during LBNP in both trials (change from Pre-LBNP to presyncope: normothermia: $+38 \pm 32$ bpm; hyperthermia: $+27 \pm 20$ bpm). In both trials, tissue SO_2 progressively decreased ($P < 0.001$) throughout LBNP (Fig. 2). However, the magnitude of this reduction was greater ($P = 0.041$) at presyncope during normothermia ($-10 \pm 6\%$) than during hyperthermia ($-6 \pm 5\%$) (Fig. 2). At 40 ± 10 mmHg LBNP, the reduction in tissue SO_2 was not different ($P = 0.803$) between trials, despite this being the average LBNP level at which presyncope occurred during hyperthermia, while tissue SO_2 continued to further decrease ($P = 0.028$) through presyncope in the normothermic trial (Fig. 2). Throughout LBNP, tVC was higher ($P \leq 0.042$) during hyperthermia than during normothermia, and this persisted through presyncope (Fig. 3).

DISCUSSION

The primary objective of this study was to test the hypothesis that hyperthermia would not affect changes in tissue SO_2

during LBNP to presyncope. Consistent with this hypothesis, reductions in tissue SO_2 were similar at each absolute level of LBNP in both normothermia and hyperthermia (Fig. 2). Counter to our expectations, however, tissue SO_2 was lower at presyncope during normothermia compared with during hyperthermia (Fig. 2). Furthermore, hyperthermia, alone, increased tissue SO_2 independent of changes in blood pressure, as evidenced by an increase in tVC (Table 1). These findings indicate that hyperthermia, alone, influences tissue SO_2 under the measurement area. Furthermore, these data also indicate that, despite tissue SO_2 being similar at absolute levels of LBNP during both conditions, the magnitude of maximal reductions in tissue SO_2 were smaller at presyncope during hyperthermia, compared with during normothermia. These data suggest that tissue SO_2 underestimates the relative magnitude of central hypovolemia during hyperthermia.

Tissue SO_2 during hyperthermia alone. In the absence of changes in metabolic rate, changes in tissue SO_2 indicate the magnitude and direction of changes in tissue blood flow (2). In the current study, tissue SO_2 increased in a similar fashion in both hyperthermic and normothermic conditions following 40–60 min of supine rest (Table 1). During normothermia, increases in tissue SO_2 were likely driven largely by increases in tissue perfusion pressure rather than alterations in vascular resistance, as indicated by elevated blood pressure without a change in tVC (Table 1). By comparison, increases in tissue SO_2 during hyperthermia were likely the result of reduced vascular resistance under the evaluated area rather than increased tissue perfusion pressure, as indicated by an elevated tVC in this thermal condition (Table 1). A possible explanation for these findings is a large (upward to 6–10-fold) hyperthermia-induced increase in skin blood flow (4, 7). Increases in muscle blood flow during hyperthermia may also contribute (18), but this finding is not always observed (10). Furthermore, a temperature-induced rightward shift in the oxygen dissociation curve cannot be discounted as a potential mechanism for

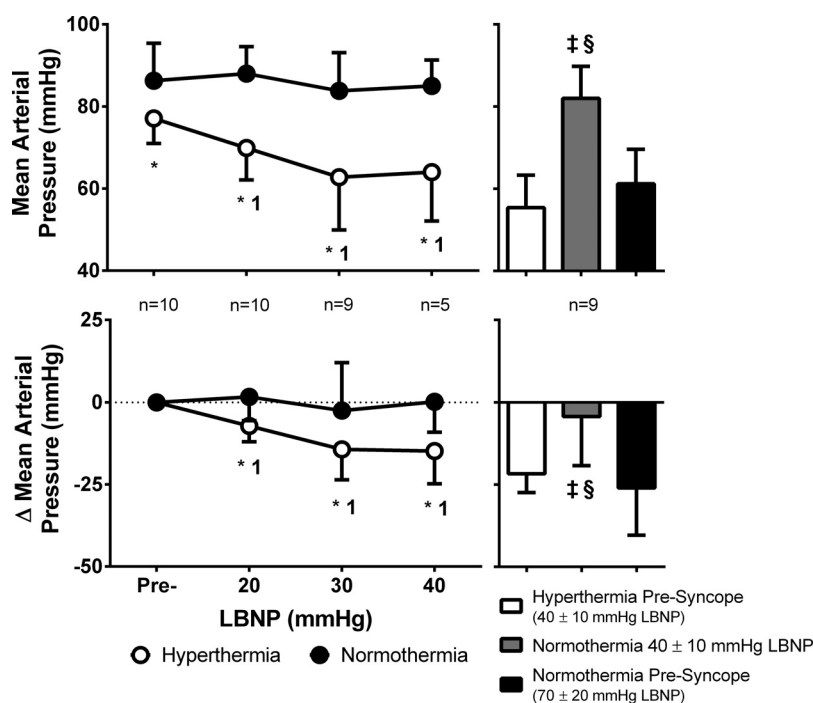
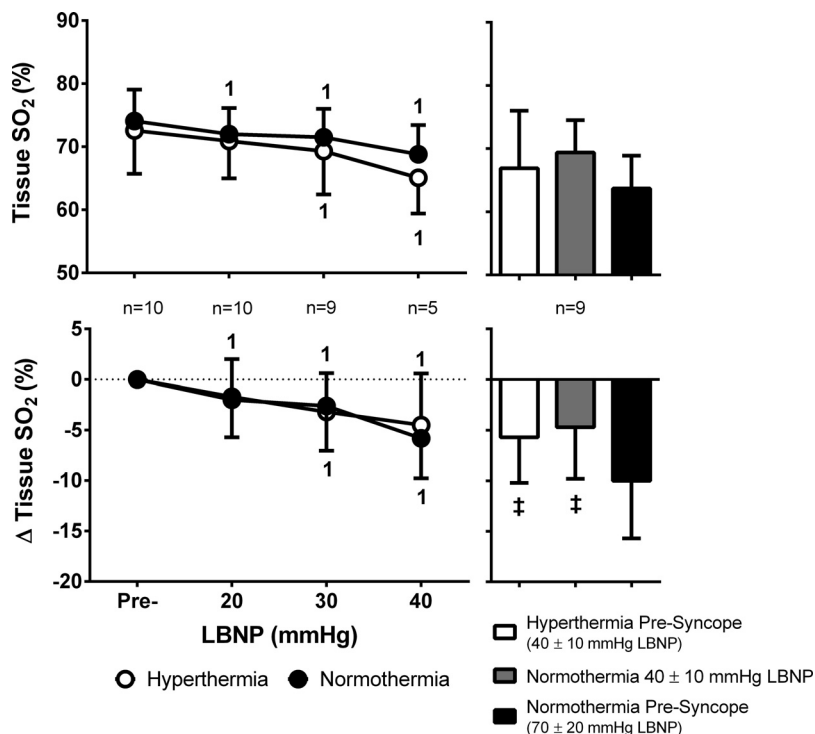


Fig. 1. Mean arterial pressure, expressed as absolute (top) and the change (Δ) from pre-lower body negative pressure (Pre-LBNP) (bottom), during normothermia and hyperthermia (means \pm SD). On the left, data are presented from Pre-LBNP through 40 mmHg LBNP, while data on the right are presented at presyncope during normothermia and hyperthermia and at the same level of normothermia LBNP as that occurring at hyperthermia presyncope, within a given subject (mean LBNP level: 40 ± 10 mmHg). n indicates the number of subjects included in the analysis at a given LBNP stage. † Significantly different from Pre-LBNP for the indicated thermal condition ($P \leq 0.005$). * Significantly different from normothermia ($P \leq 0.006$). ‡ Significantly different from normothermia presyncope ($P \leq 0.001$). § Significantly different from hyperthermia presyncope ($P \leq 0.007$).

Fig. 2. Near infrared spectroscopy-derived tissue oxygen saturation (tissue SO_2), expressed as absolute (top) and the change (Δ) from Pre-LBNP (bottom), during normothermia and hyperthermia (mean \pm SD). On the left, data are presented from Pre-LBNP through 40 mmHg LBNP, while data on the right are presented at presyncope during normothermia and hyperthermia and at the same level of normothermia LBNP as that occurring at hyperthermia presyncope, within a given subject (mean LBNP level: 40 ± 10 mmHg). n indicates the number of subjects included in the analysis at a given LBNP stage. ¹Significantly different from Pre-LBNP for the indicated thermal condition ($P \leq 0.030$). [‡]Significantly different from normothermia presyncope ($P \leq 0.041$).

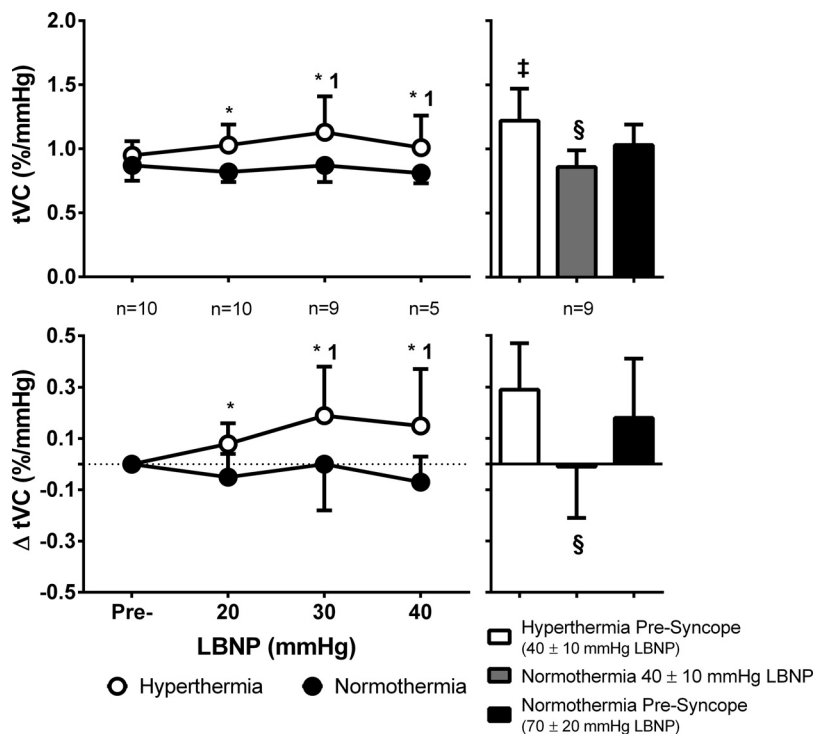


hyperthermia-induced decreases in tissue SO_2 . However, any influence of temperature on the oxygen dissociation curve is likely small given the moderate level of hyperthermia in this study (i.e., $\sim 1.2^\circ\text{C}$ increase in intestinal temperature).

Tissue SO_2 during hyperthermic LBNP. Tissue SO_2 is as an early indicator of the magnitude of central hypovolemia occurring subsequent to simulated hemorrhage in normothermic individuals (21, 22). Consistent with those observations, tissue

SO_2 progressively decreased throughout LBNP in the normothermic trial of the present study (Fig. 2). During hyperthermia, tissue SO_2 also decreased during LBNP, but at presyncope, the magnitude of the maximal reduction was lower than that occurring at presyncope during normothermia (Fig. 2). Interestingly, at the highest common LBNP stage between trials (i.e., 40 ± 10 mmHg LBNP), despite this being the level of LBNP that caused presyncope during the hyperthermic trial,

Fig. 3. Tissue vascular conductance (tVC), expressed as absolute (top) and the change (Δ) from Pre-LBNP (bottom), during normothermia and hyperthermia (means \pm SD). On the left, data are presented from Pre-LBNP through 40 mmHg LBNP, while data on the right data are presented at presyncope during normothermia and hyperthermia and at the same level of normothermia LBNP as that occurring at hyperthermia presyncope, within a given subject (mean LBNP level: 40 ± 10 mmHg). n indicates the number of subjects included in the analysis at a given LBNP stage. ¹Significantly different from Pre-LBNP for the indicated thermal condition ($P \leq 0.004$). ^{*}Significantly different from normothermia ($P \leq 0.023$). [‡]Significantly different from normothermia presyncope ($P \leq 0.042$). [§]Significantly different from hyperthermia presyncope ($P \leq 0.011$).



the magnitude of the reduction in tissue SO₂ was similar between thermal conditions (Fig. 2). Given that at this point during hyperthermia, blood pressure was profoundly lower (Fig. 1) and the magnitude of central hypovolemia is greater (6), it may be that the tissue SO₂ underestimates the relative magnitude of the central hypovolemic insult during hyperthermia. Furthermore, tVC was elevated throughout LBNP during hyperthermia (Fig. 3), suggesting that, compared with that occurring during normothermia, the vasculature under the measurement area was in a dilated state. One explanation for these observations may be due to hyperthermia-induced elevation in skin blood flow under the area of measurement (4, 7). Attenuated reductions in muscle blood flow during hyperthermic LBNP may also contribute. This contention is supported by evidence indicating that heated conduit blood vessels have attenuated vasoconstrictor capacity in vitro (12, 13) but is contrasted by in vivo evidence, indicating that muscle vasoconstrictor capacity is preserved during leg heating (15). Notably, however, the extent by which hyperthermia impacts muscle vasoconstrictor capacity currently remains unknown. Clearly, further research is required to address the mechanism(s) regarding the observed smaller reductions in tissue SO₂ at presyncope during hyperthermia.

It is interesting to note that tVC increased during the latter stages of LBNP in both trials (Fig. 3). These observations corroborate other findings, indicating that muscle vasodilation commonly precedes syncope (1). That this apparent vasodilation occurred earlier during the hyperthermia trial (Fig. 3) can likely be explained by the closer proximity of a given level of LBNP to presyncope during the hyperthermia trial compared with the normothermia trial. Although intriguing, it is important to note that these findings should be interpreted with caution, given that the utility of tVC as an indicator of tissue vascular tone during LBNP and/or hyperthermia remains uncertain.

Methodological considerations. It should be noted that the findings presented herein are likely constrained to the NIRS technology used in this study (i.e., CareGuide 1100, Reflectance Medical) and may have been different had an alternative NIRS technology been applied. Likewise, it is also notable that the clinical applicability of this technology is in its infancy. That said, although not directly related to the present study, preliminary evaluation of this NIRS technology has found that tissue SO₂ is an indicator of plasma leakage in patients with dengue hemorrhagic fever, highlighting tissue SO₂'s potential utility in a clinical setting (20).

Perspectives and Significance

Early recognition of the extent of a hemorrhagic injury and, thus, timely treatment is vital to surviving such an insult (3, 17). Noninvasive tissue SO₂ has been proposed as a valuable tool for monitoring the severity of central hypovolemia during the early stages of a hemorrhagic injury in prehospital or field settings (21, 22). However, often those individuals who are at the highest risk of a hemorrhagic injury are also hyperthermic (e.g., soldiers, miners, and firefighters). Notably, the ability to tolerate a simulated hemorrhagic event is markedly reduced during hyperthermia (19), suggesting that the timeline to begin treatment is shortened during such conditions. Therefore, the present study evaluated whether LBNP-induced reductions in tissue SO₂ were affected by

hyperthermia. It is clear that hyperthermia impacts tissue SO₂ during progressive central hypovolemia. Specifically, tissue SO₂ appears to underestimate the relative magnitude of the central hypovolemic insult during hyperthermia. Thus, it remains unknown whether a noninvasive measurement of tissue SO₂ generated from the use of NIRS technology will provide the medic with appropriate triage decision support regarding the severity of a patient's degree of central hypovolemia during hyperthermia. Further research is required.

Conclusions. Compared with that occurring during normothermia, the present study identified that reductions in tissue SO₂ during LBNP are similar with hyperthermia, but that LBNP-induced maximal reductions in tissue SO₂ are smaller at presyncope in this thermal condition. These data suggest that tissue SO₂ underestimates the relative magnitude of central hypovolemia during hyperthermia. These observations can be explained by changes in muscle blood flow and/or hyperthermia-induced elevations in skin blood flow under the measurement area. Further studies are needed to better understand the application of NIRS-derived tissue SO₂ as a noninvasive indicator of central hypovolemia during hyperthermia.

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DISCLOSURES

B.R.S. is an employee and officer of Reflectance Medical and holds stock and stock options in the company. There are no further conflicts of interest to report.

AUTHOR CONTRIBUTIONS

Author contributions: Z.J.S., E.R., and C.G.C. performed experiments; Z.J.S. analyzed data; Z.J.S., B.R.S., V.A.C., and C.G.C. interpreted results of experiments; Z.J.S. prepared figures; Z.J.S. drafted manuscript; Z.J.S., E.R., B.R.S., V.A.C., and C.G.C. edited and revised manuscript; Z.J.S., E.R., B.R.S., V.A.C., and C.G.C. approved final version of manuscript; B.R.S., V.A.C., and C.G.C. conception and design of research.

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